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Comprehensive Delineation on HIV; Latest Encroachment in Clinical Findings, Future Trends and Pharmacotherapy

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Abstract

HIV stands for human immunodeficiency virus. If HIV left untreated it may progress and develop AIDS. Once it occur human cannot rid of or relieve from it. It is cause by virus that affects immune cell that is T cells and CD4 cells. If it is not treated, it can impair many cells that fight off infections and disease. HIV infection may be identify in early stage, so we recommend prophylactic treatment that will slow the rate of virus replicate as well as linger on the onset of AIDS. Many researches are done in term of diagnosis and treatment. Researcher has discovered the protein that stimulates the resting immune cells which is infected by HIV and facilitates destruction in laboratory studies. This protein can contribute to cure HIV infection deplete the reservoir for long term, latently infected cell that can start virus formation when patient stop taking treatment. Another study stated that deficiency of Vitamin D indecently linked with an expand time to decrease CD4 count (<350 cell/μL). It is also noted there was no change in CD4 count in infected person that are not receiving ART. Many latest researchers have found and discovered vaccine for HIV but due any certain reason they were failed. Now a day's new clinical trends are made to completely cure the patient because the medication that are given or release for preventing and managing of HIV.

Keywords: HIV; AIDS; CD4 count; Vitamin D; Clinical trends; Prophylactic treatment

Introduction

Definition

HIV (Human immunodeficiency virus) is retrovirus; it infects our immune system cell, and impairs their function. Virus cause infection that leads to worsen the immune system, result in immune deficiency.

Till the end of 2014, 36.9 million people were living with this disease this is according to WHO estimation. Among them 1.2 million people dead and 2 million people were newly diagnosed or infected by HIV [1].

Types

There are two types of HIV i.e.:

- HIV 1
- HIV 2

HIV 1 is the more virulent easily transmit. HIV majority caused by HIV 1 while HIV 2 is less transmit and it is mostly confined to West Africa. HIV 2 is also called as non-progresses which mean the chance of progression into AIDS is less [2-4].

Life cycle

HIV life cycle include

- Binding
- Fusion
- Reverse transcription
- Integration
- Replication
- Assembly
- Budding.

Binding and fusion: In human HIV infect the CD4 cell. HIV gets into the cell by binding to the receptor of CD4 by the help of molecule that are present on the surface of HIV virus that is gp 120. As HIV bound with CD4, it activates protein that is present on the surface of human cell called CCR5 & CXCR4 so to complete fusion with the host cell

Reverse transcription: The RNA and other important enzyme are absorbed into the host cell (Human cell). Reverse transcriptase is viral enzyme which the process to translate its genetic material (RNA) into DNA.

Integration: The viral DNA is integrated with host cell by the help of enzyme that is integrase. It allows to re-programme the host cell to make more infected.

Transcription: In this step, two strands of DNA are divided and create a new strand of viral RNA called messenger RNA.

Translation: After that protein formation is blocked, that leads to form new HIV particle and assemble in host cell. These blocking occur due to the translation of the information that is present in the mRNA.

Vitral assembly: Protein building blocks are then break into small pieces by an enzyme called protease. From these pieces new HIV particle is form.

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Budding: Once assemble new HIV particulate buds off the host cell, and floats into the bloodstream and it is able to infect other cell means cycle start again [5,6] (Figures 1,2).

Stages

Acute infection

1. HIV infected person remains asymptomatic for a prolonged period of time, often years

2. CD4 count decline

3. It is generally occur within 2 to 6 weeks after infected with HIV

Clinical AIDS

1. Symptoms appear and many infections occur

2. CD4 count is less than 500

3. This stage last about 10 year but in some patient it may progress to last stage faster

AIDS

1. Many infections and malignancies occur

2. CD4 count is less than 200 [7]

Transmision

HIV is transmitted through different way like

- Sharing of contaminated syringes or needles
- Blood transfusion
- Unprotected sexual intercourse
- Mother to baby during breastfeeding, pregnancy and at the time of birth

People can affected by HIV will develop symptom within 5 to 10 year but this may became shorter. 10-15 years or longer time will be taken in diagnosis of HIV & AIDS. Progression of disease can be slow down by ART (antiretroviral therapy) by inhibiting the replication of virus that leads to decreasing the virus in blood of infected person (also called viral load) [8].

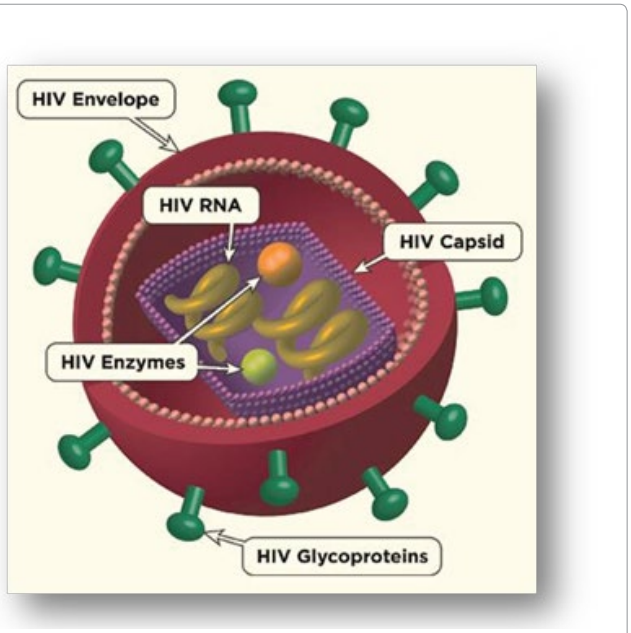

Figure 1: Structure of HIV [31].

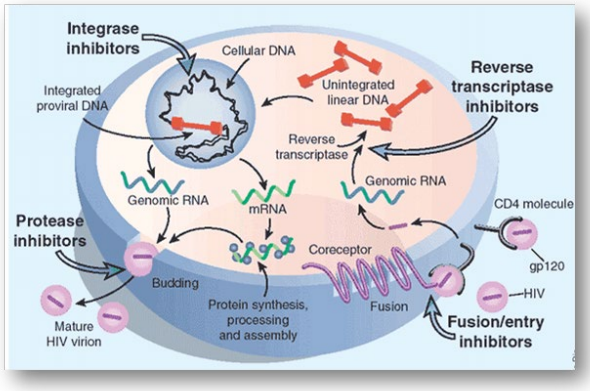

Figure 2: Life cycle of HIV [32].

Symptoms: Basically no symptoms will occur for several years. Symptoms that are developed are flu like that remain for 2-6 weeks after infected with virus.

Early symptoms (Acute)

It include; sore throat, flu, fever, chills, muscle pain, sweats, rash, enlarged glands, muscle ache, tiredness, weight loss and weakness.

Asymptomatic HIV infection (Clinical AIDS)

After initial stage mostly symptoms disappear for many years. During this period virus damages the immune system and this process can occur in 10 years. During this person appear healthy and fell well.

Late Stage HIV Infection (AIDS)

Igf HIV is not treated than it weakens the immune system. The person becomes exposed to serious illness, and it led to the stage called AIDS. Symptom includes; blurred vision, dry cough, chronic or persistent diarrhea, night sweats, shortness of breath, permanent tiredness, swollen glands lasting for weeks or white spots on the tongue or mouth. In this stage chances of developing life threatening disease increases like TB, cancer, pneumonia, etc [9-11].

Prevention

- Use condoms [12]
- Stop sharing needles [13]
- Antiretroviral therapy reduce MTCT (mother to child transmission)
- Pregnancy (medication can the harm the child. But certain treatment plan can save the baby from HIV. Avoid breast feeding and prefer bottle feeding) [14]

Medicine is also present to prevent HIV infection and they are used to prevent mother to child transmission and for PEP (post exposure prophylaxis)

Prevent transmission of HIV from mother to child: HIV infected

pregnant women should take medicine to decrease the risk of passing HIV to her child. After birth new born also recommended taking medicine for 6 months.

Post-exposure prophylaxis (PEP): After exposure to HIV, HIV medicine also reduces the risk of getting HIV.

Post-exposure prophylaxis: It is used like when any person accidentally exposed to HIV infection or having sex without safety precaution. So prophylaxis treatment must be started within three days after exposure [14-16].

Diagnosis

Standard tests: It includes blood test for checking antibodies of HIV. In response of HIV infection our body forms antibodies. This test is helpful for detecting HIV because antibodies are form after some time. Antibodies are form almost after 8 weeks but in certain cases antibodies form after 6 month time. Sometime sample are drawn from mouth or urine for screening antibodies.

Rapid antibody tests: In it also antibodies are checked. We can also detect it from saliva. Reports occur within 30minutes and it is same as standard test.

Antibody/antigen tests: By this test HIV can detect 20 days prior than standard tests. By this method we can also detect antibodies. If positive report occurs we start the treatment and avoid patient to spread infection.

Rapid antibody/antigen test: It is give report in 20 minutes.

HIV screening tests after diagnosis

CD4 count: Basically it is a protein that in present on the surface to fight against infection called T helper cell. HIV specifically targets these cells. Physician usually recommends a test of CD4 count that in a sample CD4 cells are counted. And patient with treatment must check this after 3 to 6 months.

More than 500 cells/mm^3 is the normal CD4 count. Less our immune system function lesser will be the count means increases chances or likely to have infection. When CD4 count reaches to 3200 cells/mm^3 it is said to have AIDS.

Viral load test: Mean measuring of HIV virus in blood. Low viral load indicate the treatment is effective to patient. This test is done after 2 to 4 weeks of treatment initiation. If viral load is undetectable it doesn't means person is not infected it indicate that in blood HIV virus is too low and cannot be in pick in the test.

Drug resistance testing: Sometime it is also seen that HIV doesn't treat by certain medication and can change its form. So other screening test is recommended before starting new regimen. Certain tests might include:

1. Complete blood count

2. Blood chemistry test (measure the amount of creatnine, potassium, sodium, albumin and BUN i.e. blood urea nitrogen)

3. Urine test (for kidney infection and test)

4. Cholesterol and triglyceride tests-if they are elevated it indicates HIV infection

5. Tests for other STDs (sexually transmitted diseases)

6. Tests for infections (like hepatitis, TB these are more common in patient of HIV)

Types of HIV tests

Along with other 2 test is also considered to be the most important. It include: WESTERN BLOT and ELISA (enzyme-linked immunosorbent assay). These tests are included in HIV antibody test. But this doesn't detect HIV antibodies in patient that are newly infected with it. So in this situation patient blood is tested to identify the presence of genetic material of HIV [17-20].

Treatment: In 1980s people were not live longer if they acquired AIDS. But now medication are available that is approved by FDA, 31 antiretroviral drugs are used to treat HIV infection. These drugs do not cure the patient but at undetectable level it suppresses the virus but not completely destroy the HIV virus from host body. So by this people may live longer and healthy. But to maintain the healthy patient have to take the treatment properly and on time. ART is also recommended in combination. Initially three HIV medicine is prescribe from 2 different classes. Drugs that are mentioned in Table 1 are approved by FDA for treating HIV [21].

Most recent rationalized studies

CD4 count may be rapidly decline in vitamin D deficiency usually less than 350 in untreated HIV infected person.

Vitamin D deficiency is associated with increase progression and motility of disease in HIV patient that are taken ART. But there is no proved or study that vitamins have any effect of progression of disease and CD4 count in HIV infected person but not receiving ART.

So study is conducted on 244 people and followed this for 11 month. 42% are seems to have deficiency of Vitamin D. CD4 count of healthy individuals were 502 cells/μL and the infected patient seems to have an increased risk of decrease CD4 count i.e. < 350 cells/μL. HR (hazard ratio) is 95%. So it is concluded that deficiency of Vitamin D independtly linked with an expand time to decrease CD4 count (< 350 cell/μL). It is also noted there was no change in CD4 count in infected person that are not receiving ART [28].

Now recently treatment of HIV include pills that should be taken daily so scientist develop the new regimen which have long lasting effect and it could be administer once or twice/ year. So scientist investigated and invented a new delivery system that is named as Nano-formulauted Protease Inhibitor. In this process they took drug and make its crystal .these crystal are placed in protein coat and fats which protect the drug from degradation by liver and elimination by kidney. And this was tested along with URMC-099 in the laboratory of scantiest Harris. A so it is noted that measurable quantity of HIV was eliminated by PI (protease inhibitor). URMC-099 prolongs the therapeutic effect decrease the concentration and also boosted the concentration of drug in immune cells. The reaction between antiretroviral and URMC-099 increases the duration, reduce general toxicity and improve patient complains. These therapies are tested in laboratory on human immune cell and in mice. It is the belief of scientist that this technology will help to keep the PI in white blood cell and life span extends due to URMC-099 [28].

Another research in the field of HIV treatment is done in which scientist found protein that activates the infected cell; this protein is called VRCO7-αCD3 which triggered the Inhibition and killing of latently infected T cell it is observe when cells are taken from the patient that are on antiretroviral therapy and treated in laboratory with

Drug Class	Mechanism of Action	Generic Name
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)	Reverse transcriptase enzyme block by NRTIs. From these enzyme HIV make its copies	abacavir (abacavir sulfate, ABC) didanosine (delayed-release didanosine, dideoxyinosine, enteric-coated didanosine, ddI, ddI EC) emtricitabine (FTC) lamivudine (3TC) tenofovirdisoproxil fumarate (tenofovir DF, TDF) zidovudine (azidothymidine, AZT, ZDV)
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	It binds and alters reverse transcriptase enzymes.	delavirdine (delavirdinemesylate, DLV) efavirenz (EFV) etravirine (ETR) nevirapine (extended-release nevirapine, NVP) rilpivirine (rilpivirine hydrochloride, RPV)
Protease Inhibitors (PIs)	HIV protease is blocked by PIs.	atazanavir (atazanavir sulfate, ATV) darunavir (darunavirethanolate, DRV) fosamprenavir (fosamprenavir calcium, FOS-APV, FPV) indinavir (indinavir sulfate, IDV) nelfinavir (nelfinavirmesylate, NFV) ritonavir (RTV) saquinavir (saquinavirmesylate, SQV) tipranavir (TPV)
Fusion Inhibitors	It inhibit HIV from entering the CD4 cells.	enfuvirtide
Entry Inhibitors	It inhibits the protein that is present on CD4 cells. From these proteins HIV enter in cells.	maraviroc (MVC)
Integrase Inhibitors	Integrase inhibitors, inhibit HIVintegrase enzyme.	dolutegravir (DTG) elvitegravir (EVG) raltegravir (raltegravir potassium, RAL)
Pharmacokinetic Enhancers	It is used just to increase the effectiveness of HIV treatment or regimen.	cobicistat (COBI)
Combination HIV Medicines	Combine two or more drugs of one or more classes are given in combination.	abacavir and lamivudine (abacavir sulfate / lamivudine, ABC / 3TC) abacavir, dolutegravir, and lamivudine (abacavir sulfate / dolutegravir sodium / lamivudine, ABC / DTG / 3TC) abacavir, lamivudine, and zidovudine (abacavir sulfate / lamivudine / zidovudine, ABC / 3TC / ZDV) atazanavir and cobicistat (atazanavir sulfate / cobicistat, ATV / COBI) darunavir and cobicistat (darunavirethanolate / cobicistat, DRV / COBI) efavirenz, emtricitabine, and tenofovirdisoproxilfumarate (efavirenz / emtricitabine / tenofovir, efavirenz / emtricitabine / tenofovir DF, EFV / FTC / TDF) elvitegravir, cobicistat, emtricitabine, and tenofovirdisoproxilfumarate (QUAD, EVG / COBI / FTC / TDF) emtricitabine, rilpivirine, and tenofovirdisoproxilfumarate (emtricitabine / rilpivirine hydrochloride / tenofovirdisoproxilfumarate, emtricitabine / rilpivirine / tenofovir, FTC / RPV / TDF) emtricitabine and tenofovirdisoproxilfumarate (emtricitabine / tenofovir, FTC / TDF) lamivudine and zidovudine (3TC / ZDV) lopinavir and ritonavir (ritonavir-boosted lopinavir, LPV/r, LPV / RTV) [21-27]

Table 1: Drugs used in HIV [21].

the patients killer T cells. This protein inhibits the activation and killing of latent T cell that are infected by HIV. This protein has 2 ends:

• One it binds with T cells on CD3 receptor and activates the cell

• Other depends on antibodies commonly called VRCO7 it is strongly bind to HIV strain 90%.

The engineered protein have two sides: one activates T cells by binding to a surface molecule called the CD3 receptor, and second-based on an antibody called VRC07-powerfully binds to more than 90 percent of HIV strains. VRC07-αCD3 increases the killing of latently HIV-infected cells in three steps. First, the CD3-binding end attaches to a resting, HIV-infected T cell, activates the cell so it starts making HIV and displaying pieces of virus on its surface. The HIV-binding end of the protein latches onto those pieces of virus while the CD3-binding end attaches to a T cell (killer), activating it and bringing it close to the helper T cell. Finally, the activated killer T cell destroys the HIV-infected helper T cell. Figure 3 shows that how protein works in destroying the infected immune cell.

• Cells and protein, the yellow one is protein and black is CD3 binding while HIV binding is shown by thick black, red for killer T Cell that is inactivated and in blue HIV infected helper T cell.

• On helper T cell CD3 receptor binds to protein, activate the T cell so that it form HIV and show the virus (red) on surface

• On killer T cell protein binds with CD3 receptor and on helper T cell protein binds to HIV fragment , which cause activation of killer T cell and these 2 cell come close together

• Helper T cell that is infected by HIV is destroying by the activation of killer T cell [29].

Upcoming treatments

Many latest researchers have found that made many vaccines for HIV but due any certain reason they were failed. Now a day's new clinical trend are made to completely cure the patient because the medication that are given or release for preventing and managing of HIV (Tables 2,3) [30].

Conclusion

Treatment strategy for HIV infection are age-specific .Over the recent years many advancements are takes place in the management of HIV, here we discussed some of the latest researches on gene therapy, CD4 count ,upcoming treatments and causes and precautions of this life threatening disease. There is still some need of researches to put

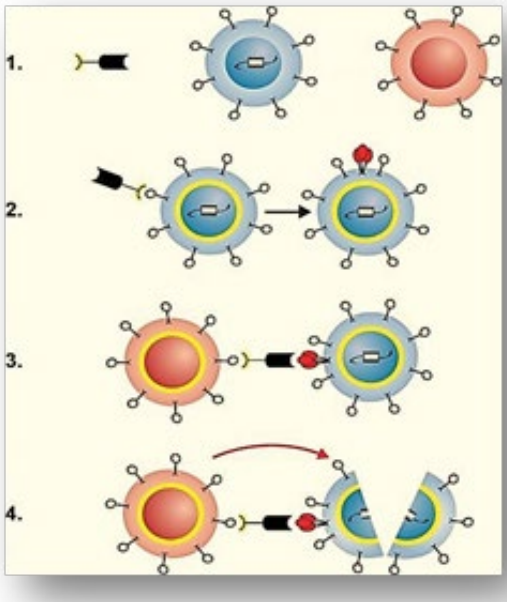

Figure 3: Engineered protein facilitates destruction of latently HIV-infected immune cells [33].

Trial	Trial Registry Identifier(s)	Manufacturer/Sponsor(s)	Phase	Published/Presented Data
THERAPEUTIC VACCINES				
DermaVir (topically applied DNA vaccine)	NCT00711230	Genetic Immunity	Phase II	N/A
DermaVir	NCT00918840	Genetic Immunity	Phase II	N/A
GSK Biological HIV Vaccine 732462 (p24-RT-Nef-p17 fusion protein vaccine)	NCT01218113	GlaxoSmithKline	Phase II	N/A
Tat protein vaccine	NCT01513135	Barbara Ensoli, MD, IstitutoSuperiore di Sanità/ Italian Ministry of Foreign Affairs - General Direction for Cooperation and Development	Phase II	N/A
Tat Protein Vaccine	NCT01513135	Barbara Ensoli, MD, IstitutoSuperiore di Sanità	Phase II	Retrovirology. 2015 Apr 29;12(1):33 PLoS One. 2010 Nov 11;5(11):e13540
Vacc-4x (peptide-based vaccine)	NCT00659789	BionorImmuno AS	Phase II	Lancet Infect Dis. 2014 Apr;14(4):291-300
VAC-3S (peptide-based vaccine)	NCT01549119	InnaVirVax	Phase I/IIa	30 Years of HIV Science, 2013, poster abstract 145 IAS 2015 Towards an HIV Cure Symposium,Poster Abstract PE67 LB
Dendritic cell vaccine	NCT00833781	Massachusetts General Hospital	Phase I/II	N/A
Autologous HIV-1 ApB DC Vaccine	NCT00510497	Sharon Riddler, University of Pittsburgh/NIAID	Phase I/II	N/A
Dendritic Cell Vaccine (DCV-2)	NCT00402142	Hospital Clinic of Barcelona	Phase I/II	SciTransl Med. 2013 Jan 2;5(166):166ra2
DermaVir	NCT00270205	AIDS Clinical Trials Group	Phase I/II	JAIDS. 2013 Dec 1;64(4):351–9

TUTI-16 (synthetic HIV-1 Tat epitope vaccine)	NCT01335191	Thymon, LLC	Phase I/II	Hum VaccinImmunother. 2012 Oct;8(10):1425-30
Vacc-C5 (peptide-based vaccine)	NCT01627678	BionorImmuno AS	Phase I/II	N/A
D-GPE DNA + M-GPE MVA (DNA + viral vector vaccines)	NCT01881581	Centers for Disease Control and Prevention, China	Phase I	N/A
JS7 DNA + MVA62B(DNA + viral vector vaccines)	NCT01378156	GeoVax, Inc.	Phase I	HIV R4P 2014,Abstract OA05.03 (webcast)
MAG pDNA vaccine+/- IL-12	NCT01266616	NIAID	Phase I	N/A
AT20-KLH	MED-AT20-001	Medestea Research & Production SpA, Turin	Phase I	Vaccine. 2014 Feb 19;32(9):1072-8
AFO-18 (peptide-based vaccine)	NCT01141205	Statens Serum Institut (SSI)/Ministry of the Interior and Health, Denmark/European and Developing Countries Clinical Trials Partnership (EDCTP)	Phase I	AIDS Res Hum Retroviruses. 2013 Nov;29(11):1504-12
AFO-18 (peptide-based vaccine)	NCT01009762	SSI/Rigshospitalet/Hvidovre University Hospital/ Ministry of the Interior and Health, Denmark	Phase I	ClinImmunol. 2013 Feb;146(2):120-30
Dendritic cells loaded with HIV-1 lipopeptides	NCT00796770	Baylor Research Institute/ANRS	Phase I	Retrovirology 2012, 9(Suppl 2):P328
DermaVir	NCT00712530	Genetic Immunity	Phase I	PLoS One. 2012 7(5): e35416
HIV-v (peptide-based vaccine)	NCT01071031	PepTcell Limited	Phase I	Vaccine. 2013 Nov 19;31(48):5680–6

Table 2: Latest Treatments [30].

Trial	Trial Registry Identifier(s)	Manufacturer/ Sponsor(s)	Phase	Published/Presented Data
GENE THERAPIES				
Cal-1: Dual anti-HIV gene transfer construct	NCT01734850 NCT02390297 (long term safety phase)	Calimmune	Phase I/II	June 2015 January 2032
VRX496 (gene-modified autologous CD4 T cells)	NCT00295477 (closed to enrollment)	University of Pennsylvania	Phase I/II	December 2020
MazF-T (redirected MazF-CD4 autologous T cells)	NCT01787994	Takara Bio/University of Pennsylvania	Phase I	December 2016

Table 3: Some gene therapy is also used for the treatment of HIV [30].

forward for its better cure management in order to make patient's life improved and easier. Selection of the drug regime should be appropriate through proper monitoring of the disease this could be achieved so far. Guidelines for pediatric populations are compiled by the Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children; guidelines for adults and adolescents are compiled by the Panel on Clinical Practices for Treatment of HIV Infection.

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30. HIV VACCINE AND CURE RESEARCH HIGHLIGHTS FROM IAS 2015 July 23, 2015 • 0 comments • By Miguel Gomez, Director, AIDS.gov, and Senior Communications Advisor, Office of HIV/AIDS and Infectious Disease Policy, U.S. Department of Health and Human ServicesAs the 8th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2015) came to a close in Vancouver, Canada, we spoke one last time by Skype with Dr. Carl Dieffenbach, Director of the Division of AIDS at NIH's National Institute of Allergy and Infectious Diseases (NIAID), to learn about some of the highlights. Throughout the conference, he reports, researchers shared information about various scientific pathways that may bring us to both an HIV vaccine and a cure.
31. https://aidsinfo.nih.gov/images/factsheet/HIV-virus-03.jpg
32. https://aidsinfo.nih.gov/images/factsheet/HIV-lifecycle-05.jpg
33. http://images.sciencedaily.com/2015/10/151020145233_1_540x360.jpg